Submission of evidence to show beneficial antimicrobial effects of the claimed formulation

Introduction

- The study was carried out by SGS Life Science Services, Singapore and sponsored by Hygieia Healthcare Limited
- The report putting forth the interim analysis of the results of the study was prepared on 8 November 2006.
- Infections are central to flare-ups and maintenance of the Atopic Dermatitis condition. This is integral to and helps mediate the inflammatory response associated with Atopic Dermatitis. Bacterial infections are predominantly caused by Staphylococcus aureus, the majority of which secretes toxins with superantigenic properties.
- There is a substantial body of data demonstrating that atopic dermatitis and various other skin diseases are associated with disturbances of skin barrier function as evidenced by an increase in transepidermal water loss (TEWL), a decrease in water-binding properties, and a reduction in skin surface lipids, specifically levels of ceramides. The loss of this natural defence further exacerbates the disease, thus perpetuating the ongoing cycle.
- The product being tested is a cream with triclosan as the active ingredient present in an amount of 1wt% of the formulation
- The other ingredients in the product used in the study are the same as the antimicrobial barrier formulation of Table 2 of the present application with silicon at about 1wt% and the viscosity of the formulation being less that 20 Pascal second.

Objectives of study

- The primary objective of the study was to demonstrate the safety and effectiveness of the cream with an effective amount of triclosan compared to the Vehicle cream for the treatment of atopic dermatitis cause by microbial infection.
- Other objectives of the study were to demonstrate that the test cream having an effective amount of triclosan prevents a relapse of atopic dermatitis, to demonstrate that test cream significantly decreases trans-epidermal water loss and to assess the cosmetic acceptability of the test cream.

Design of Study

- The study comprised a double single centre, randomized, controlled trial to compare the test cream comprising 1% triclosan with a Vehicle having for the treatment of atopic dermatitis caused by microbial infection.

- The composition of the test cream used in the study was same a the composition of the barrier formulation described in Table 2 of the accompanying description for the present invention The amount of triclosan in the formulation for the study was chosen to demonstrate its effectiveness against a Vehicle cream with the same ingredients but without triclosan and also to exhibit that the antimicrobial activity of triclosan in the range specified in the present application.

Methodology

- Twenty (20) subjects were included in the study: 10 used the test cream, and the other 10 used the Vehicle cream. All 20 subjects completed the study, and all subjects were included in the interim analysis.

- All subjects were also given topical corticosteroid cream containing 0.025% betamethasone valerate to use in place of other corticosteroid medications during the study. Therefore, all subjects received either test cream with 0.025% betamethasone valerate or vehicle cream with 0.025% betamethasone valerate. The use of low concentration preparation containing 0.025% betamethasone valerate in place of other corticosteroid medications during the study was to ensure that the subjects in the test cream group or the vehicle group do not suffer adverse effects due to complete stoppage of earlier corticosteroid medication.

- The usage of the low concentration of steroid (0.025% betamethasone valerate) was assumed to be equal in both arms, and hence the effect was cancelled off during statistical analysis.

- The median (min-max) age of the patients in the study was 18 (12-24) years. A quarter of the subjects was female (5/20). All subjects but one were Chinese. The remaining subject was Indian.

- The median (min-max) SCORAD* score at baseline was 36.30 (11.6-54.0). Both groups were comparable with respect to the SCORAD score. The median (min-max) age of onset of atopic dermatitis was 6 (1-17) years. The median (min-max) duration was 120 (6-216) months. The majority (17/20) of the currently included subjects had moderate atopic dermatitis. Of note, the 3 subjects with mild atopic dermatitis all received the vehicle cream.

Results

- Primary efficacy parameter: response at day 27

  Response was defined as a decrease in SCORAD of at least 20 units. In the test group, 6/10 (60%) subjects responded at day 27, versus 2/10 (20%) in the vehicle group. This treatment difference of 40% is in favour of the test cream, and matches the expected difference of the protocol's sample size calculation.

  At day 14, half of the test subjects (5/10) already showed a response. At that moment, none of the vehicle subjects had responded. At day 41, 4/10 of the test subjects responded versus 3/10 of the Vehicle subjects.

- Secondary efficacy parameter: change from baseline at day 27 in SCORAD

  The mean (SE) SCORAD decreased from 33.70 (3.828) at baseline to 16.49 (2.766) at day 27 for the test cream, and from 33.42 (4.569) to 18.92 (4.602) for the vehicle. This corresponds to a mean (SE) SCORAD change from baseline at day 27 of –17.21 (3.844) for the test cream and –14.50 (2.618) for the Vehicle, so in advantage of the test cream.

* In order to evaluate the severity of this disease as objectively as possible, the European Task Force on Atopic Dermatitis has developed a method allowing consistent assessment by means of a severity index called **SCORAD** (for **SCO**ring **A**topic **D**ermatitis).

Discussion

- The study clearly exhibited that the test cream with 1wt% triclosan is more effective in the treatment of atopic dermatitis caused by microbial infection than a Vehicle creamwithout any triclosan.

- The unique mechanism by which the test cream works, is to use an active therapeutic moisturizing vehicle, that in effect retains Triclosan at its intended site of action for a prolonged period. Therefore both its antimicrobial and anti-inflammatory effects are given time to have a significant clinical impact. Due to the interrelated nature of both the inflammation and infection, this phenomenon along with prolonged moisturizing has a synergistic effect, to provide a highly effective treatment to alleviate the symptoms of Atopic Dermatitis.

- It was determined that the increased efficacy of the test cream is due to the antimicrobial properties of triclosan in the test cream. In addition, triclosan has some anti-inflammatory properties and will therefore target the key factors mediating and maintaining the atopic disease state.

- The antimicrobial activity of triclosan is attributable to the presence of an effective amount of triclosan in the barrier formulation. It has been determined that triclosan present in a composition in low amounts such as 0.3% by wt of the formulation will have negligible effect on the treatment of atopic dermatitis due to its insufficient anti microbial activity.